There is no suggestion in Gleisner that all f-Met peptides are effective inhibitors of degranulation. Nor is there any suggestion that the presently claimed f-Met-Leu peptides inhibit degranulation. Table 1 at page 20 of the present specification clearly shows that all f-Met-Leu peptides are not inhibitors of degranulation. Indeed, the presently claimed f-Met-Leu peptides exhibit surprising and unexpected degranulation inhibition properties.

It is not seen how one of ordinary skill in the art would reasonably expect the present invention in view of Gleisner.

The Oxford dictionary of Biochemistry and Molecular Biology (1981) fails to make up for the deficiencies of Gleisner. Although it teaches that mast cells are important in the development of allergenic response, there is no teaching or suggestion that all f-Met-Leu peptides are not inhibitors of degranulation. Nor is there any teaching or suggestion that the presently claimed f-Met-Leu peptides exhibit surprising and unexpected degranulation inhibition properties.

Dumitrascu and Casale also fail to make up for the deficiencies of Gleisner.

Thus, it is not seen how it would have been obvious to one of ordinary skill in the art to use the presently claimed f-Met-Leu peptides to treat allergy.

Kermode et al. teach that various f-Met peptides are potent stimualtors of degranulation. Indeed, Kermode et al. teach that both f-Met-Leu-Phe and f-Met-Leu-Phe-Phe are potent stimulators of degranulation of neutrophils are chemotactic. Thus, Kermode et al. not only fail to make up for the deficiencies of Gleisner, but also provide teachings contrary to Gleisner. Such characteristics and pro-inflammatory activity would lead one skilled in the art away from the use of the presently claimed f-Met-Leu peptides to treat allergy.

Anderson also fails to make up for the deficiencies of Gleisner. Table 1 of the present specification illustrates the so-called "core structure" proposed by the examiner does not provide each compound with the same bioactivity. Nothing in Anderson teaches or suggests the surprising degranulation inhibiting activity of the presently claimed f-Met-Leu peptides. The examiner concludes that one would expect that the formyl Met peptide would activate functions of neutrophils. However, that is a pro-inflammatory response and not desirable. One skilled in the art would not use such a peptide that activates neutrophils for treating allergy.

Ferry also fails to make up for the deficiencies of Gleisner. Ferry recognizes f-Met peptides as pro-inflammatory peptides. Thus, it is not seen how it would have been obvious to one of ordinary skill in the art to use the presently claimed f-Met-Leu peptides to treat allergy.

It is respectfully submitted that one of ordinary skill in the art would have been led away from the present invention by the cited prior art.

Claim 3 is rejected under 35 U.S.C. 103(a) for the reasons dset forth with respect to claims 1 and 2, and further in view of Goodman and Gilman ("AL"). Goodman and Gilman fail to teach or suggest the use of the presently claimed f-Met-Leu peptides to treat allergy. thus, it is not seen how the presently claimed invention would have been obvious to one of ordinary skill in the art from any combination of the cited prior art.

The Kermode reference is an attempt to prove the following mechanism by which formyl peptides stimulate neutrophil degranulation and chemotaxis (page 715,

column 2, lines 3-15):

> One proposal for the neutrophil is that the **high-affinity form of the receptor** may be responsible for activation of some biological functions, notably chemotaxis, with the **low-affinity form** responsible for other functions, e.g. degranulation. Similar proposals have been made to explain the differential activation of a range of biological responses in several other cell types and with several other receptor agonists. The only evidence to date to support this hypothesis for the neutrophil, however, is derived from studies of the influence of various perturbations of the cell on both the receptor-binding pattern and the biological responses for a single chemotactic formyl peptide, the prototypical compound N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMet-Leu-Phe). [Emphasis added].

Kermode tests several different formyl peptides, including f-Met-Leu-Phe, and categorizes them into "most potent" and "less potent". Furthermore, Kermode concludes that the "most potent" peptides bind to the high affinity form of the receptor, and that the "less potent" peptides bind to the low affinity form of the receptor. The "most potent" peptides according to Kermode are f-Met-Leu-Phe-Phe and f-Met-Leu-Phe-NHBzl. The "less potent" peptides are f-Met-Leu-Phe, f-Nle-Leu-Phe, f-Nva-Leu-Phe and f-Val-Leu-Phe. Thus, even amongst formyl peptides, according to Kermode, there are differences in potencies and in their mechanism of action.

Kermode, however, makes **no** suggestion for using formyl peptides for any therapy . There is not even a hint of a suggestion by Kermode that such peptides will be useful for any therapeutic treatment.

In fact, Ferry teaches that administration of low molecular weight formyl peptides is **pro**inflammatory and, by whatever route, could cause **unwanted reactions or disorders**. For example, Ferry states on page 64, second column under Discussion:

> There is an increasing body of evidence suggesting that low molecular weight **proinflammatory** N-f-met oligopeptides **could play a role in intestinal inflammatory disorders**. All species of intestinal bacteria so far investigated produced such peptides in vitro and bioactive peptides have been demonstrated in colonic fluid obtained by in vivo dialysis techniques.
>
> In experimental animals **both colonic infusions and rectal administration of N-formyl methionyl-leucyl-phenylalanine (N-f-met-leu-phe) resulted in experimental colitis**, although the concentrations used in these studies were in the millimole range, at least three orders of magnitude greater than those estimated by bioassay of intestinal contents.
>
> **Systemic infusion** of radiolabeled f-met peptides in rats showed that intact peptide was rapidly excreted in bile and an enterohepatic circulation of f-met peptide was subsequently demonstrated. **Experimental acetic acid-induced colitis was associated with an eightfold increase in biliary excreation of labeled peptide following its instillation into colon loops**. [Emphasis added].

Ferry concludes from their own experimental data that (page 61, first column, lines 19-28):

> in the ileum both enzymic degradation and restricted mucosal permeability contribute to the intestinal barrier to luminal bacterial formyl oligopeptides. In the colon, however, enzymic mechanisms are less active and restricted mucosal permeability is the major factor. **Abnormalities of the intestinal mucosal barrier to proinflammatory bacterial peptides could play a role in inflammatory disorders of the gut**.

Although their conclusion focuses on administration of formyl peptides to the **unhealthy** intestine, they also suggest problems even if administered to **healthy** individuals. Ferry admits that their failure to find increased absorption to the intestine under normal conditions cannot in any way be used even to assume, much less to predict with reasonable certainty, that these peptides will have no adverse effect when administered to healthy individuals (paragraph bridging pages 65-66):

> **Changes in vascular permeability and blood flow (without changes in mucosal permeability) have been reported with f-met-leu-phe in rat small intestine** by Granger et al. and these effects were apparently not found in animals rendered neutropenic, suggesting an effect of f-met-leu-phe on neutrophil leukocytes in the microcirculation of the gut. More recently, **the same group reported increased mucosal permeability in response to ileal perfusion with f-met-leu-phe (10^{-6}M)**. This observation supports that of Magnussen et al. The effect appears to be confined to the terminal ileum and to be leukocyte-dependent. **We failed to find increased ^{51}Cr-EDTA absorption with either f-met-leu-tyr (10^{-4}M) or f-met-leu-phe (10^{-4}M) alone over a 1-h period. The short period of observation and the infusion into loops rather than perfusion design may account for this. Our studies were simply designed as controls for our experiments with different agents rather than to investigate the inflammatory response and permeability changes secondary to leukocyte accumulation. Trace amounts of intact formyl peptides do escape the enzyme and mucosal permeability barriers and trace amounts of intact peptide (picomoles) were recovered in bile in our control studies**. The biological significance of these amounts awaits further studies. [Emphasis added].

Ferry suggests that the trace amounts of formyl peptide in bile **may be** a symptom of potential adverse effects even under healthy conditions but has not investigated this issue. However, based on the wealth of information provided by others, one of ordinary skill in the art would consider it is likely.

Indeed, for example, Kermode teaches, contrary to Gleisner, that (page 1991, right column):

> [t]he logical interpretation of these data is thus that the high-affinity sites are the receptors that **initiate degranulation**. (Emphasis added.)

Because Kermode also teaches that f-Met-Leu-Phe-Phe binds to the high affinity receptor, one skilled in the art would be expected to conclude that f-Met-Leu-Phe-Phe **initiates degranulation** of the neutrophils and thus is harmful.

Earlier Kermode postulated that the high affinity site was responsible for

activiating chemotaxis, which also is harmful. Thus, it is not seen how any teaching of Kermode would lead one of ordinary skill in the art to make a pharmaceutical composition as claimed herein. Indeed, the first discovery that the claimed f-Met peptides provide useful biological properties was made by Applicant. Indeed, this useful property has been found only in the few claimed peptides, not in all f-Met peptides.

Ferry supports Kermode in teaching that f-Met peptides cause harmful effects. In view of these teachings, why would one of ordinary skill in the art even consider the use of f-Met peptides in a pharmaceutical composition. Indeed, althought there are extensive publications relating to f-Met peptides, to Applicant's knowledge, none of them suggest administering such peptides for any beneficial effect.

The studies of Anderson also support the notion that formyl peptides and their analogues may **cause inflammatory disorders** and thus **would not be useful** as pharmaceutical compounds. For example, Anderson first recites the types of disorders that may be associated with formyl peptides and then suggests a mechanism for the cause of such disorders (page 249, first column, lines 1-10; page 254, second column, lines 32-41):

> **There is now a substantial body of evidence implicating bacterial F-met peptides in intestinal inflammatory disorders**. They induce adhesion, chemotaxis, superoxide production, and lysosomal enzyme release in neutrophil leukocytes; **can induce experimental colitis** in mice, rats, and rabbits; **increase intestinal vascular and mucosal permeability**; stimulate intestinal leukotriene synthesis; and are **spasmogenic for gut smooth muscle**.***
>
> Using a radioimmune assay with a rabbit polyclonal antibody raised against FMLP, we have identified FMLP immunoreactivity in both rat and human bile. The most likely source of this reactivity is formyl oligopeptide produced by intestinal bacteria and reaching the liver in portal blood. **Since the liver excretes such peptides in a largely unaltered form, they presumably retain their potential to induce inflammatory responses should they cross the biliary epithelium**.

[Emphasis added].

Anderson concludes that (page 255, column 1):

> The association between biliary tract disorders and inflammatory bowel disease has long been thought to be related to the presence of bacterial products in bile, **and low-molecular-weight formyl-peptides could be important in this respect**. [Emphasis added].

Thus, the Anderson reference also **teaches away** from using formyl peptides and their analogues as for therapy.

Thus, given the many teachings that f-met peptides are harmful and corresponding the lack of incentive to administer the f-Met peptides for therapeutic effect, one of ordinary skill in the art would not have been motivated to make and use a pharmaceutical compound for the formyl peptides of the present invention. As noted by Kermode (as cited above), local and systemic administration of f-Met peptides have both been associated **to induce** intestinal inflammatory disorders.

In view of the above, it is not seen how the present invention would have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejections are requested.

It is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Respectfully submitted,

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